The problem
Epigenetic programing in the first 1000 days: Stress caused by nociception is a major factor.

Since conception, each new life starts to prepare itself to live. During Epigenetic programing in the first 1000 days, the autonomic nervous system (ANS) develops to allow new life to survive in its environment (1). Adverse events may lead to epigenetic changes, with implications for health and disease.

The number of preterm infants is increasing; These babies are fragile as they are born with a weak parasympathetic system (2). Newborns in the NICU may undergo more than 12 painful procedures per day, which puts them in a state of continuous stress, worsening their outcomes (3,4). Babies who experience a lot of stress during the first 1000 days of life have been shown to be at higher risk for physical and psychological problems, such as hypertension (5), diabetes (6), or behavioral problems such as alcohol abuse (7) or mental health disorders.

*HF: High Frequency

Picture modified from Hugues P. et al. (2)
POTENTIAL EFFECTORS
Hormones, neurotransmitters, growth factors, nutrients
Epigenetics (DNA methylation, histone modifications, microRNAs)

PRECONCEPTION
Egg/sperm development/maturation

GESTATION
Placental development/function
Organ development
Neuronal development

POST NATAL
Brain maturation/function
Immune function
Reproductive function

OFFSPRING PHENOTYPE
Brain morphology/function
Physiological function
Behavior

MATCHED ENVIRONMENT
Promote health

MISMATCHED ENVIRONMENT
Predispose to pathology/disease

Picture modified from Moore E et al. (8)

Picture from Boersma JG. et al. (4)
It is crucial to measure the well-being of these babies to allow them to be as comfortable as possible. However, pain assessment in neonates is extremely challenging, pain scales are subject to inter-observer differences, each neonate may display different signs of pain leading to different interpretations and different results among observers (9), in addition they are time consuming to perform. Hence, a more objective, fast, reliable and easy to use physiological measure is needed.

Measuring the autonomic nervous system (ANS)

The NIPE (Newborn Infant Parasympathetic Evaluation) monitor measures inter-beat distances of the R-R intervals derived from the ECG. These distances vary due to heart rate variability (HRV): the influence of respiration on the vagus nerve.

Analyzing the signal derived from HRV produces a metric (HFnu), indicating the relative of parasympathetic activity in the previous minutes.

*Picture modified from Debillon T et al. (9)
The NIPE value shows continuously and objectively the parasympathetic activity of the patient. A NIPE of 53 corresponds to a Comfort Behavioral Scale (CBS) score > 17 (10).

Assessment of Procedural Distress in Sedated/Intubated Children Under 3 Years Old Using the Newborn Infant Parasympathetic Evaluation: A Diagnostic Accuracy Pilot Study

Interpretation of NIPE

Relationship of NIPE with CBS – Picture modified from Morgan R. et al. (10)
The result

Dr. Walas validated the NIPE in an observational study, showing the NIPE value decreases more depending on the intensity of the stimulation (11). Faye PM et al. proved that Low NIPE values corresponded to high EDIN scores and vice-versa (12).

NIPE detecting different pain intensities

Moreover, in NICU’s implementing the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) NIPE can be used to evaluate the favorable impact of cocooning (13) and skin to skin contact (14) on the preterm infant.

NIPE in assessing the impact of NIDCAP maneuvers

Using NIPE will allow evaluation of the state of comfort/discomfort of the patient. This case study is an example where oral saccharose was given in advance to an infant increasing NIPE value and after the heel prick resulted in a decrease in the NIPE (15).

NIPE on skin to skin contact

Impact of skin-to-skin contact on the autonomic nervous system in the preterm infant and his mother

NIPE detecting the effects of saccharose during heel stick

Internal case report (15)
The main benefits of using NIPE technology

NIPE shows the sympathetic/parasympathetic balance allowing taking better decisions to control nociception improving outcomes (17).

**Testimonials**

**Dr. Wojciech Walas**  
Head of Anesthesiology and Intensive Therapy for Children and Neonates  
University Hospital in Opole, Poland

“**The Goldilocks principle, that means not too little, but not too much. NIPE and ANI help me optimize analgosedation in my patients.**”

**Dr. Itziar Marsinyach Ros**  
Neonatology Assistant Physician  
Hospital Gregorio Marañón, Madrid

“A tool to measure parasympathetic tone, through heart rate variability, could be useful to assess both the state of comfort and the maturity of the autonomic system in the premature newborn.”

**Dr. Hector Boix**  
Neonatal Research Coordinator  
Vall d’Hebron University Hospital, Barcelona

“**Thanks to NIPE we have an objective parameter to assess stress in our neonatal ICUs.**”
Bibliography:


(15) Internal case report
